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Passive cigarette smoke–challenge studies: Increase in bronchial hyperreactivity

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Degree and duration of bronchial hyperreactivity (BHR) after environmental tobacco smoke (ETS) inhalation was assessed in 31 smoke-sensitive subjects with asthma who exhibited lower airway symptoms on ETS exposure (group I) and 39 smoke-sensitive subjects without asthma who manifested only upper airway symptoms on cigarette-smoke exposure (group II). Subjects were challenged with ETS for 4 hours in a static-test chamber. The atmosphere was continuously monitored for airborne particulate levels (800 cpm), total suspended particulates (1266 ± 283 μg/m³), and airborne nicotine levels (226 ± 49 μg/m³). Methacholine challenges were performed before and serially after cigarette-smoke exposure, and the provocative dose causing a 20% fall in FEV_1 was determined. Five of the 31 smoke-sensitive subjects with asthma and none of the smoke-sensitive subjects without asthma reacted to cigarette-smoke challenge (≥20% fall from baseline FEV_1). Thirty-two percent (10/31) of the subjects with asthma demonstrated increased BHR at 6 hours, 29% (9/31) at 24 hours, and 13% (4/31) up to day 14 after ETS challenge. Of the subjects without asthma, 18% (7/39) demonstrated increased BHR at 6 hours, 10% (4/39) at 24 hours, and 8% (3/39) at 3 weeks. These studies demonstrated an increase in BHR after cigarette-smoke challenge in a number of study subjects (although they were clinically asymptomatic) and suggest that prolonged subclinical airway inflammation can occur in the absence of demonstrable change in airway caliber on exposure to ETS. (J ALLERGY CLIN IMMUNOL 1992;89:560-6.)

Key words: *Environmental tobacco smoke, bronchial hyperreactivity*

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Several inhalation-challenge studies have assessed the response of adult subjects with asthma to passive cigarette-smoke exposure.[1-4] Although some of the studies[1, 2] failed to demonstrate an appreciable decline in pulmonary function, other studies[3, 4] reported a significant decline FEV_1 in groups of nonsmoking subjects with asthma after controlled challenge with ETS. Rechallenge studies of these subjects 24 months later with ETS confirmed our previous observation and suggested that "sensitivity" to ETS was persistent.[5] Classic late-phase reactivity (at 5 to 6 hours after challenge) was not demonstrable, and cromolyn sodium and/or albuterol protected the airways from the effects of ETS.[5]

Abbreviations used

ETS:	Environmental tobacco smoke
BHR:	Bronchial hyperreactivity
MC:	Methacholine challenge
TSP:	Total suspended particles
cpm:	Counts per minute
SS:	Smoke-sensitive
PD_{20}:	Provocative dose of methacholine causing a 20% decrease in FEV_1

Increased bronchial reactivity has been previously reported in a group of smokers with normal pulmonary function.[6] Furthermore, increased nonspecific BHR has been noted among children with asthma with smoking mothers.[7-9] Increase in BHR is the hallmark of late-phase airway reactivity.[10, 11] Increase in BHR has also been demonstrated after isolated early pulmonary response,[12] suggesting that airway caliber per se does not influence the response to methacholine.

Reactivity to ETS is unique, occurs after 60 or more

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minutes of continuous cigarette-smoke exposure, and does not represent classic immediate or late pulmonary reactivity.[5] The present study was designed to assess and characterize any increase in BHR after a single ETS challenge. This was achieved by serial MCs administered before and after passive cigarette-smoke exposure.

MATERIAL AND METHODS

Subjects

Subjects with asthma and control subjects without asthma were recruited from the respondents to a newspaper advertisement announcing the study. Subjects with asthma met the definition of asthma of the American Thoracic Society. Subjects had a positive MC and/or ≥15% increase in FEV_1 after bronchodilator administration. Thirty-one SS subjects with asthma (12 to 50 years of age, 21 black and 10 white subjects; 11 were male and 20 were female) and 39 subjects without asthma (aged 12 to 50 years; 21 black and 18 white subjects; 17 were male and 22 were female) participated in the study. All subjects were "smoke sensitive" in that the subjects with asthma reported chest tightness, shortness of breath, cough, or wheezing, and the subjects without asthma reported only upper respiratory symptoms on exposure to ETS. All subjects gave informed consent and answered a questionnaire specifying degree and duration of symptoms, medications, past medical history, smoking history, exposure to passive cigarette smoke (work or home), and personal assessment of sensitivity to cigarette smoke. A physical examination was performed on all study subjects.

Skin tests

All subjects were prick skin tested with a panel of 25 common seasonal and environmental allergens (house dust, mite, ragweed, grasses, trees, and molds), two tobacco-leaf extracts (the first, 1:10 wt/vol, from Hollister-Stier, Elkhart, Ind., and the second, 10 mg/ml, prepared in our laboratory from the tobacco of 1R4F cigarettes) and a cigarette-smoke extract prepared by bubbling 1R4F cigarette smoke through phosphate-buffered saline.[13] Subjects demonstrating two or more positive skin tests to seasonal and environmental allergens (≥3 mm wheal from the saline control) were considered atopic.

Pulmonary-function tests

Baseline pulmonary functions (FEV_1, FVC, peak expiratory flow rate, $FEF_{25\%-75\%}$) were performed with a Pulmonaire (Jones Medical Instrument Co., Oak Brook, Ill.) spirometer with a datamite 3 microprocessor. Baseline peak flow was recorded by each subject after challenge with a mini-Wright peak flow meter (Clement Clarke International, Ltd., London, England).

Inhalation methacholine challenges

All bronchodilators were withheld for 12 hours, and cromolyn sodium and antihistamines were withheld for 24 hours before the MC. Preparation of methacholine solution, production and characterization of aerosol, method of inhalation, measurement of lung function during challenge, and the full MC protocol used in this study have been previously described.[4, 14] MC was done according to the technique described by Chai et al.[5] with some modifications.

The full protocol comprised of 12 sequential doubling cumulative doses and used 10 doubling concentrations of methacholine (in Phenol-buffered saline solution) from 0.0625 to 32 mg/ml. The various concentrations of methacholine were delivered via a mouthpiece with a DeVilbiss (DeVilbiss Co., Somerset, Pa.) No. 45 nebulizer. Each nebulizer was attached to a compressed-air source at 20 psi, producing, with the air vent closed, an outlet flow of 11.0 ± 0.1 L/min. The length of each nebulization was controlled by a nebulization dosimeter (Rosenthal-French, The Johns Hopkins University, Baltimore, Md.) at a setting of 0.6 seconds per inhalation. After baseline measurements of FEV_1 (100% equals mean of six readings), sequential challenges were administered with the diluent control and doubling cumulative doses of methacholine from 0.3 unit (1 unit, one inhalation of aerosol from a 1 mg/ml solution of methacholine) to maximum of 640 cumulative units. The test was terminated when a 20% decrement of mean FEV was sustained for 5 minutes or the maximal methacholine dose had been administered. Any bronchoconstriction was then reversed by inhaled albuterol. The cumulative dose of methacholine that corresponded to a 20% decrease in FEV_1 was determined by linear interpolations of the last two points on the dose-response curve.

Study subjects who had no respiratory infections in the last 4 or more weeks before the test and demonstrated at least 70% of predicted FEV_1, were subjected to MC on the afternoon of the day before the ETS challenge. The following day, ETS challenges were performed and serial MCs were done on all subjects at 6 and 24 hours after the passive cigarette-smoke exposure. Since there was very little variation of PD_{20} of subjects not exposed to ETS, for the purpose of the study, a twofold or greater decrease in PD_{20} was considered to be a significant increase in BHR after smoke exposure. Subjects demonstrating a significant increase in BHR at 24 hours were followed with serial MCs on days 3 and 7 and weekly thereafter until the subjects' PD_{20} methacholine returned to pre-ETS-challenge levels. As control subjects, 10 subjects with asthma were subjected to three serial MCs (0, 6, and 24 hours) without challenging the subjects with cigarette smoke.

Cigarette-smoke inhalation challenge

Challenge chamber. The static-test chamber used for challenges was 3.66 by 2.13 by 3.35 m with a 26 m^3 volume. A temperature of 21° to 24° C and relative humidity of 50% to 60% was maintained throughout the challenge procedures. Air circulation was provided by a portable fan. Smoke-generating equipment, air-sampling equipment, and the spirometer were in the chamber.

ETS challenge. The study protocol was approved by the Human Experimentation Committee of Tulane University Medical Center. All participants gave written informed consent. Subjects underwent ETS challenge while their asthma was "stable" (without any recent flares for the previous 3

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months, hospitalizations, upper respiratory tract infections, or significant adjustments in asthma medications). Medications were withheld according to the established guidelines.[10] Details of the ETS challenge have been previously published.[4] After baseline pulmonary functions (FEV_1, FVC, peak expiratory flow rate, $FEF_{25\%-75\%}$), subjects were exposed for 4 hours (starting between 8 AM to 9 AM) to mixed mainstream-sidestream cigarette smoke from 1R4F reference cigarettes (Tobacco Research Institute, University of Kentucky, Lexington, Ky.) generated with a Borgwaldt fully automatic smoking machine (Heinrich Borgwaldt, Hamburg, Germany). The subjects could not be blinded during challenge because it was impossible to mask cigarette-smoke exposure. Eighteen to 24 cigarettes were smoked during the course of a 4-hour challenge to maintain airborne particulate level of 800 cpm, as measured by a Sibata P5 (MDA Scientific, Lincolnshire, Ill.) continuous aerosol monitor. If the study subjects demonstrated a ≥20% drop from baseline FEV_1, the subject was considered a reactor, was allowed to exit from the chamber, and was administered nebulized albuterol. After ETS challenge, subjects were observed in the laboratory for a total of 10 hours. Hourly peak flow determinations were performed with a mini-Wright peak flow meter for an additional 14 hours after the subject returned home to identify any late-phase responses.

Quantitation of cigarette-smoke exposure during inhalation challenge

The level of cigarette-smoke exposure during bronchoprovocation challenge was determined by measuring relative particulate levels, airborne nicotine, and TSP levels as previously described.[4] Relative particulate levels (expressed as counts per minute) were continuously monitored with a Sibata model P5H2 light-scattering aerosol indicator (MDA Scientific) during the challenge. Integrated samples of the particulates were collected at a flow rate of 1 L/min on preweighed 37 mm Teflon FA filters (Millipore, Milford, Mass.) for gravimetric quantitation of TSP concentration. Quantitation of airborne nicotine was based on modification of the method proposed by the National Institute for Occupational Safety and Health.[17] Nicotine was collected on XAD-4 resin tubes (SKC, Inc., Eighty-four, Pa.) at a sampling rate of 1 L/min. Absorbed nicotine was desorbed with 1 ml of mobile phase (85:15:0.1/hexane: *n*-propanol: triethylamine), filtered and analyzed by high-performance liquid chromatography on a 30 cm microporasil column (Waters Associates, Milford, Mass.) and quantitated by ultraviolet absorbance at a wave length of 265 nm.

RESULTS

Study population

The questionnaire survey indicated that of the subjects with asthma, 25 were receiving inhaled β_2-agonist, 16 were taking oral theophylline, three were taking cromolyn sodium and steroid inhalers, and seven subjects were taking antihistamines. Six of the SS subjects without asthma were taking antihistamines. Eighty-four percent of the SS subjects with asthma and 92% of the SS subjects without asthma never smoked. The remaining subjects were all exsmokers for at least 4 years. Sixty-one percent of the SS subjects with asthma and 49% of the SS subjects without asthma claimed exposure to passive cigarette smoke at home or the workplace. All subjects were atopic.

Only 11% of the subjects reacted to either of the tobacco-leaf extracts. None of the subjects had a positive test of cigarette-smoke extract. There was no correlation between positive skin test to tobacco-leaf extract and cigarette-smoke reactivity or increase in BHR.

Cigarette-smoke challenge

The study subjects were exposed to mixed mainstream-sidestream smoke. During the 4-hour ETS challenge, airborne particulate levels of 800 cpm were maintained that resulted in a TSP of 1266 ± 283 $\mu g/m^3$ and airborne nicotine level of 226 ± 49 $\mu g/m^3$.

Five of the 31 SS subjects with asthma reacted (≥20% fall from baseline FEV_1) on ETS challenge. These five subjects demonstrated persistent reactivity to ETS on repeated challenges for at least 3 consecutive years. No classic late-phase pulmonary response was demonstrated in any of the study subjects monitored with a mini-Wright peak flow meter for 24 hours from the commencement of ETS challenge. None of the 39 SS subjects without asthma demonstrated a significant decline in pulmonary function during or after 4-hour ETS challenge.

Methacholine challenge

Thirty-two percent (10/31), 29% (9/31), and 16% (5/31) of the SS subjects with asthma demonstrated increased BHR at 6 hours, 24 hours, and 3 days, respectively, after ETS challenge (Fig. 1). Sixteen percent (5/31) and 13% (4/31) of the SS subjects with asthma had increased BHR at 1 week and 2 weeks after ETS challenge. One SS subject with asthma demonstrated a 16-fold increase in BHR at 6 and 24 hours after ETS challenge; two other SS subjects with asthma demonstrated 11-fold and eightfold increases in BHR at 24 hours. In one SS subject with asthma, the increase in BHR persisted for 8 weeks. Four SS subjects with asthma requested the use of inhaled albuterol at 6 and/or 24 hours and were not further methacholine challenged. Five SS subjects with asthma demonstrated a greater increase in BHR at 24 hours than at 6 hours after ETS exposure. None of the 10 control subjects challenged with three serial

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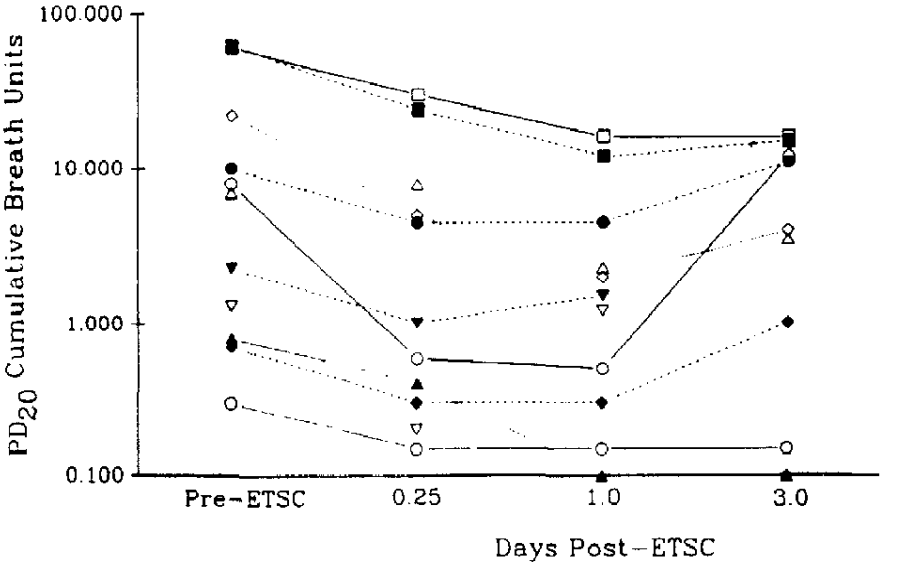

FIG. 1. Methacholine PD_{20} (cumulative breath units) before and at 6 hours, 24 hours, and 3 days after ETS challenge in SS subjects with asthma who demonstrated increased BHR. Each *symbol* represents an individual's response.

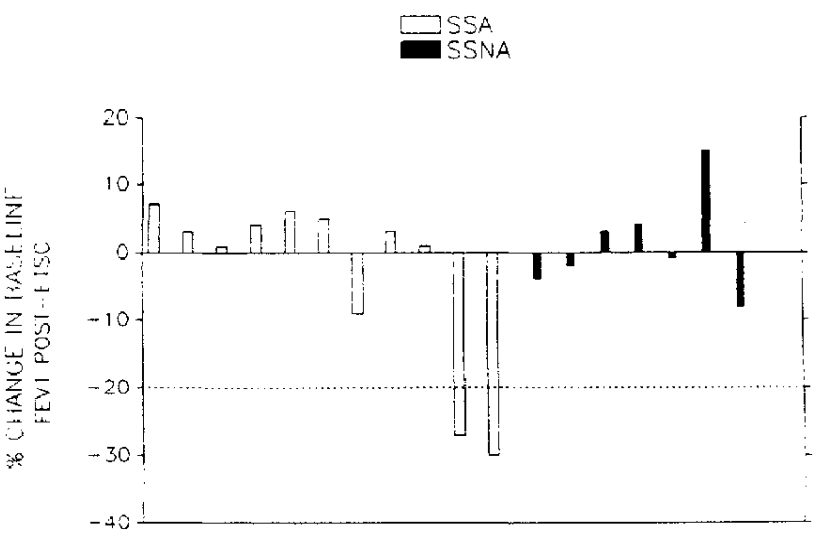

FIG. 2. Change in FEV_1 of study subjects who demonstrated increase in BHR after ETS challenge. *Dotted horizontal line* indicates a positive response to ETS by 20% or more drop in FEV_1 from baseline.

MCs without cigarette-smoke exposure demonstrated a twofold or greater decline in PD_{20}. The change in baseline FEV_1 on the study subjects who demonstrated increased BHR after ETS challenge is illustrated in Fig. 2.

Of the SS subjects without asthma, 18% (7/39) and 10% (4/39) demonstrated increased BHR at 6 and 24 hours, respectively (Fig. 3). Increased BHR persisted in 2/39 SS subjects without asthma for up to 3 weeks. One SS subject without asthma demonstrated in-

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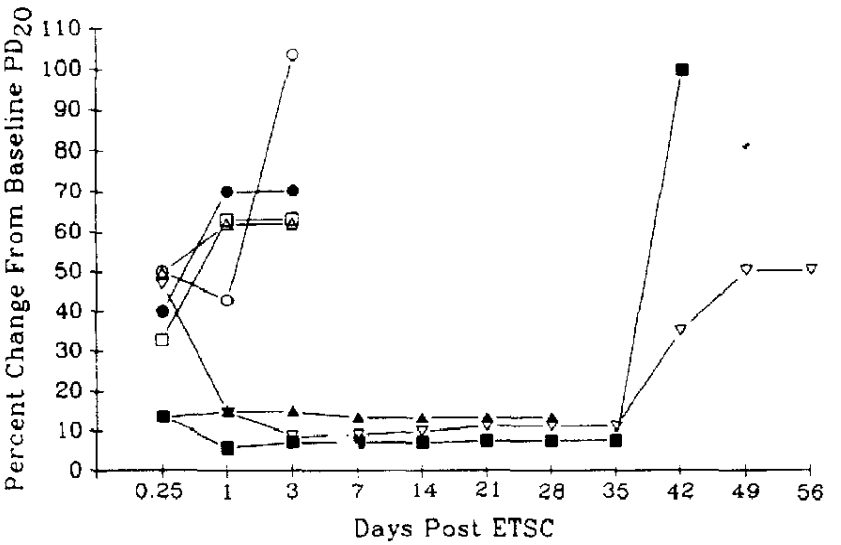

FIG. 3. Change in methacholine PD_{20} in SS subjects without asthma after ETS challenge. *Y axis* denotes percent change in post-ETS challenge PD_{20} from Pre-ETS challenge PD_{20}. *X axis* is the time interval after ETS challenge in days. *Zero* on the *Y axis* is equal to pre-ETS challenge PD_{20}, which was different in the various study subjects. *Each symbol* represents an individual's response.

creased BHR for up to 8 weeks after single ETS exposure.

DISCUSSION

Our studies of passive cigarette-smoke challenge in nonsmokers demonstrate that almost 1/3 of SS subjects with asthma and 1/5 of SS subjects without asthma have a marked increase in BHR 6 hours after ETS exposure. The increase in BHR varied. One subject with asthma had a 16-fold increase in BHR. Two other subjects, one subject with asthma and one without, each had increased BHR that persisted for up to 8 weeks after cigarette-smoke exposure. These increases in BHR were observed in spite of an absence of demonstrable late-phase pulmonary responsiveness and appreciable change in airway caliber on spirometry. However, the fact that all subjects were atopic may limit the applicability of these results to the general population. Degree of bronchial reactivity before ETS challenge had no apparent impact on the outcome of ETS challenge.

It is of particular interest that an increase in BHR was observed in asymptomatic subjects without asthma after ETS exposure. Since "dose" and duration of passive cigarette-smoke exposure may have been important factors in their responses, every effort was made during the challenge to simulate ETS levels similar to levels encountered in real life. The cigarette-smoke levels used in our bronchoprovocation studies have been reported in public places.[18] However, as is the case with allergen challenges, the subjects may have been exposed to relatively higher doses of ETS in a shorter period of time during challenge. Some of the subjects demonstrated increased BHR for prolonged periods of time (8 weeks). This finding could be due to ongoing cigarette-smoke exposure at home, work, or elsewhere. Six of 11 subjects with asthma and two of seven without asthma who demonstrated increased BHR reported cigarette-smoke exposure at home or work.

The precise mechanism(s) of ETS-induced increase in BHR is unknown. Possibly it involves irritant parasympathetic receptors. Studies with animal models[19] have demonstrated that inhalation of volatile organic chemicals, such as toluene diisocyanate, increases airway reactivity induced by substance P and decreases airway neutral endopeptidase activity, perhaps by injuring or destroying epithelial cells. It would be worthwhile to investigate the role of neuropeptides and their inhibitors in the induction of ETS-induced BHR. In vitro studies have suggested that cigarette smoke stimulates release of neutrophil chemotactic factor activity from cultured bronchial epithelial cells,[20] which could, in turn, lead to chronic inflammation. The fact that an anti-inflammatory agent, such as cromolyn sodium, could protect the airways from the effects of cigarette smoke[5] also argues in favor of low-grade chronic subclinical airway inflammation induced by ETS. Irre-

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spective of the mechanism(s) involved, our current findings raise the possibility that inhaled environmental chemicals and volatile pollutants can induce airway hyperreactivity in the absence of antecedent overt clinical symptoms. Perhaps the cumulative efforts of such exposure could lead to a permanent state of airway hyperreactivity or even a condition resembling "intrinsic" asthma. It is also theoretically possible that ETS-induced airway inflammation could increase epithelial permeability and thereby increase the likelihood for IgE sensitization. This may explain the reported association of active tobacco smoking with an increase in serum IgE levels[21] and eosinophil counts.[22]

The nature of the ETS component inducing BHR has not been identified. Is it possible that nicotine is responsible for the induction of BHR after ETS exposure? Our challenge atmospheres had a nicotine to TSP ratio of 1:6, which is in the upper range for such ratios commonly observed in public places.[23] It is unlikely, however, that nicotine is related to any increase in BHR since recent in vitro studies[24] have demonstrated that hyperreactivity induced by cigarette smoke is not due to an acute effect of nicotine on airway smooth muscle or to an interaction between muscle and epithelium.

The relative contribution of the particulate and gaseous phase of cigarette smoke in inducing BHR is not clear and requires further study. We have demonstrated that significant levels of upper and lower respiratory tract irritants, such as formaldehyde, acrolein, acetaldehyde, NH_3, and NO_2 are present in the gaseous phase in the test chamber.[25] Bronchoprovocation with gaseous phase of cigarette smoke in a dynamic test chamber, planned for the future, will address this issue. The relative contribution of mainstream versus sidestream cigarette smoke in induction of BHR is unknown since all subjects in the present study were challenged with mixed mainstream-sidestream cigarette smoke. In preliminary results from another study in our laboratory with another group of 20 subjects with asthma, 30% have, however, demonstrated increased BHR after challenge with sidestream cigarette smoke alone.

Whether or not serial MCs within a 24-hour period per se may alter airway susceptibility to subsequent MCs can be questioned. Prior methacholine administration has not been demonstrated to increase responsiveness to subsequent MCs.[26] On the contrary, a decrease in responsiveness to methacholine has been reported in nonsmoking subjects without asthma serially challenged with methacholine within 24 hours or less.[27] None of the 10 control subjects with asthma in this study who were subjected to three sequential MCs within a 24-hour period, without ETS exposure, demonstrated a twofold or greater decline in PD_{20} as occurred in some of the subjects after ETS challenge.

Clearly, passive cigarette-smoke challenge studies performed in the laboratory are limited by experimental conditions and thus cannot always be equated with ETS exposure in real life situation. However, we believe that our finding of increased mecholyl-induced BHR after ETS exposure, even in asymptomatic subjects, is relevant to the issue of cigarette-smoke reactivity. Allergen avoidance has been demonstrated to decrease BHR and improve symptoms in a group of subjects with asthma,[28] and it is possible that a similar beneficial effect could occur by avoidance of ETS.

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